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A Review of the Most Significant Components of the Evaluation and Management of Primary Urethral Carcinoma

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ABSTRACT:

Primary urethral carcinoma (PUC) is a rare malignancy with limited treatment options. The purpose of this overview is to outline current strategies for this patient setting. Most of the current literature contains retrospective studies with small sample sizes and non-intuitive treatment instructions. The difficulty in treating this disease begins with diagnosis. Proximal (posterior) tumors may be missed until late in the disease because they are difficult to palpate during the physical examination. Early-stage distant tumors may also be misdiagnosed as infections, delaying treatment and potentially worsening prognosis. Our patient was diagnosed as having primary urethral cancer in the First Clinical Hospital of Yichang by cystoscopy and biopsy. Due to her advanced age, poor health and economic conditions, she refused to undergo radical surgery. Since there is no clear guideline for the treatment course of primary urethral cancer clinically, different hospitals have different surgical methods and postoperative concomitant treatments, resulting in different prognosis effects. Additional studies with standardized treatment approaches for patients, preferably in a randomized prospective controlled setting, are needed to advance evidence-based treatment approaches.

Introduction

Primary urethral carcinoma (PUC) is a rare malignancy, accounting for less than 1% of all malignancies (1). The annual incidence in the United States is 4.3 per 1 million men and 1.5 per 1 million women (2). The three major histologic subtypes of PUC are urothelial carcinoma (UC), squamous cell carcinoma (SCC), and adenocarcinoma (AC) (3). Current standards for treating PUC are not well established and consensus is needed on the best therapeutic strategies to treat PUC (4). Urothelial carcinoma (UC) is the most common histologic type in men, accounting for 47-73% of PUCs. Squamous cell carcinoma accounts for 12-30% and adenocarcinoma accounts for 5-16% [5,6,7]. UC is also the most common histologic type in women, accounting for approximately 45% of PUCs, although adenocarcinoma is more common than squamous cell carcinoma at 29% and 19%, respectively [8]. Dirksen et al. We also confirmed that adenocarcinoma was the most serious malignancy, followed by squamous cell carcinoma and transitional cell carcinoma [8]. This can be explained by the fact that adenocarcinoma likely arises as lymph node metastasis, leading to disease progression [8]. Early diagnosis of PUC is of great importance for clinical management, as this early-stage cancer has no obvious symptoms and lacks specific screening indicators. In the middle and late stages, there are some obvious symptoms, such as: B. Dysuria, dyspareunia, irritation, haematuria, etc. Several types of tests are used to diagnose PUC, including magnetic resonance imaging (MRI) and computed tomography (CT), but cystoscopy and biopsy are the most accurate. Given the low prevalence of this cancer, there are no uniform standards for the management and treatment of PUC, and different hospitals have different treatments for different histological PUC types. Less than 1% of all malignancies are primary urethral carcinomas (PUC), a rare malignant tumour. According to the Surveillance, Epidemiology and End Results (SEER) registry, the annual incidence of PUC in men and

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women in Europe is estimated to be 1.6 per million and 0.6 per million, respectively, with an age-standardized ratio, whereas in the USA it is 4.3 per million and 1.5 per million [9,10]. The highest incidence rate was among African Americans (3.33/1 000 000), then among Caucasians (1.72/1 000 000), Hispanics (1.57/1 000 000), and other racial groups (1.57/1 000 000) [11]. The SEER program conducted an analysis, and it found that PUC incidence peaked in people over 75. According to an analysis by the SEER program, the peak incidence of PUC was in the more than 75 years of age group (7.6 per million) and almost negligible in ages less than 55 years [12].

2. Diagnostic assessment

2.1. Clinical history

Early on, PUC patients might not exhibit any distinct symptoms and might be misdiagnosed with more typical urethral strictures, particularly if they are female. More than 70% of women report recurrent urinary tract infections, irritable voiding symptoms, or dyspareunia. Once diagnosed, the majority of female patients would have T3-4N0M0 stage disease (29%) whereas the majority of male patients would have T1N0M0 stage disease (32%) [13]. More importantly PUC patients would initially face with visible hematuria or bloody urethral discharge symptoms. Locally sophisticated PUC patients(T3 / T4)(45 %e57 %) may face with furthermore symptoms, as an example an extra-urethral mass, bladder outlet any hindrance, pelvic sting, urethrocutaneous fistula, abscess formation, or dyspareunia[14].

2.2. Clinical examination

Clinical evaluation of patients included digital rectal examination in males and pelvic examination with urethral palpation in females. In males, suspected hardening of the external genitalia can be palpated or probed through physical examination with a finger through the rectum. In women, bilateral inguinal palpation should be performed to assess local clinical staging to assess the presence of enlarged lymph nodes (LN) with determination of location, size, and mobility [20]. A bimanual examination should also be performed to determine the local clinical stage and exclude the presence of colorectal or gynaecological malignancies [21].

2.3. Urinary cytology

Cytological assessment of urine specimens could be utilized to locate the PUC with sensitivity of 50 %e80 % [22]. Detection rates of urinary cytology depended on the pathological write. For male patients, the sensitivity values for urothelial carcinoma (UC) and squamous cell carcinoma (SCC) were stated to be 80 %and 50 % , respectively.in the meantime for female patients, the sensitivity values for UC and SCC were found to be 50 %and 77 % , respectively[23].

2.4. Cytological assessment of urine specimens

Cystoscopy and urethral biopsy can be used to assess the extent of the urethral tumor, its location, and the underlying histology [23]. Biopsy sites (proximal or distal) should be marked and sent to the pathologist with clinical information. Urethral cystoscopy can also be used to rule out associated bladder tumors, since urethral cancer can also originate in the bladder via micrometastases [24]. Transurethral resection of larger lesions can be performed for histological diagnosis. In patients with suspected ulcerative urethritis or prostatic ducts, resectoscopic biopsy of the prostatic urethra can be helpful in diagnosing ulcerative prostatitis, as described in more detail below.

2.5. Diagnosis of UC of the prostate

The American Joint board on Cancer developed a TNM staging treat specifically for PUC (Table 1) [15,16]. The T is positive by the how much of tumor invasion, N is amount of lymph node involvement, and M is a measurement of the amount of metastasis. This TNM method is establish with the aim of quantify the how much of PUC involvement in a patient to be utilized as an algorithm key for expanding a treatment approach. The diagnosis and staging of PUC are positive by a mixture of physical exam, imaging, and biopsy (Figure 1) [17] .

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Table 1: Reprinted with permission from the American Joint Committee on Cancer—TNM tumor staging for urethral cancer (15). T refers to the extent of tumor invasion, N refers to the extent of lymph node involvement, and M refers to the extent of metastasis

Stages	Details
T stage	
Tx	Tumor cannot be assessed
Tis	Carcinoma in situ
Ta	Non-invasive carcinoma
T1	Lamina propria invasion
T2	Spongiosum, prostate, or periurethral muscle invasion
T3	Cavernosum, vagina, or bladder neck invasion
T4	All regional nodes are negative
N stage	
N0	All regional nodes are negative
N1	Single positive node <2 cm
N2	Single positive node >2 cm or multiple nodes
M stage	
M0	No metastasis
M1	Distant metastasis

Grading of urothelial urethral carcinoma

PUNLMP	Papillary urothelial neoplasm of low malignant potential
Low grade	Well differentiated
High grade	Poorly differentiated

Grading of nonurothelial urethral carcinoma

Gx	Tumor grade not assessable
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated

TNM = tumour-node-metastasis; WHO = World Health Organization.

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PUC has been disorderly and hard to discover, so this tumor is frequently not detected unless after stages [18]. common methods for detecting PUC signify physical exam, cystoscopy with confirmatory tissue biopsy, and imaging. The elusiveness and rarity of this malignancy may make it overlooked unless after stages—delaying treatment unless it manifests into sophisticated disease therefore reducing generally speaking survival. Since there exist more determined responses with before time juncture and asymptomatic PUC [18,19], it's optimal to find these tumors before time in advance of symptoms occur. Bimanual examination ought to be carried out for local clinical staging and to exclude the presence of colorectal or gynaecological malignancies [21].

2.6. Diagnostic imaging

Radiographic imaging can help assess local tumor extent and detect lymphatic spread and distant metastases in patients with urethral carcinoma. A combination of tumor biopsy, magnetic resonance imaging (MRI), and computed tomography (CT) can help in the diagnosis and classification of urethral cancer [25]. Regarding imaging, computed tomography (CT) of the chest, abdomen and pelvis is strongly recommended to assess soft tissue and lymph node involvement and to identify distant metastases. CT scans should include pre- and post-contrast images and time-delayed series to allow assessment of the entire urinary tract. Recently, the literature has shown that magnetic resonance imaging (MRI) is a superior imaging modality for assessing disease onset due to its high sensitivity in assessing local tumor involvement and response to chemoradiotherapy [26,27].

3. Treatment of PUC

The male urethra is divided into anterior (shoe bone sinus, penile and bulbar urethra) and posterior (membranous urethra, prostatic urethra). Lymphatic vessels from the anterior urethra drain sequentially to the superficial and deep inguinal lymph nodes and then to the pelvic (external iliac) lymph nodes, while lymphatic vessels from the posterior urethra drain to the pelvic lymph nodes [28].

Male urethral tumours are generally classified based on location and histology. The bulbomembranous urethra is most commonly affected, accounting for 60% of tumours, followed by the penile urethra and the prostate. Rabbani's SEER study showed that urothelial carcinoma (77.6%) made up the majority of primary urethral carcinomas, followed by squamous cell carcinoma (11.9%), adenocarcinoma (5%) and other histologist (5th and 5th).5%).[29] Tumor histology also varies with the location of the urethra: carcinomas of the prostatic urethra are primarily urothelial/transitional cell carcinomas, while penile and bulbomembranous carcinomas of the urethra tend to be scaly.[30]

Men with UKA may have symptoms that make urination difficult or irritating, such as B. dysuria, decreased urinary flow, urinary retention and perineal urethral pain, Urethrocutaneous stricture or fistula [20,31-32].

The female urethra is much shorter than the male, being generally 3-4 cm long. It is divided into anterior (distal one-third) and posterior (proximal two-thirds), which is an important distinction when considering surgical treatment. The proximal third of the female urethra is lined with urothelial transitional epithelium, while the other two-thirds are lined with stratified squamous epithelium. The lymphatic vessels of the posterior urethra in women drain into the pelvic lymph nodes (internal, external, and obturator lymph node chain), while the urethra and labia minora in women drain into the superficial and then the deep inguinal lymph node. [33]

In contrast to urethral cancer in males, PUC in the female typically occurs along the entire length of the urethra.[34] Furthermore, with regards to histology, urothelial carcinoma is the most common tumor type in female PUC (30–45%), followed by adenocarcinoma (29%) and squamous cell carcinoma (19–28%) according to SEER data and a study from the Netherlands National Cancer Registry [6,35]. The incidence rate of adenocarcinoma (0.26–1.4 cases/million person years; PY) is higher than urothelial carcinoma (0.12–0.7 cases/million PY) and squamous cell carcinoma (0.12–0.76 cases/million PY) among females age 35–64. However, among women 65–84 years of age, the incidence rate of adenocarcinoma (1.5–1.6 cases/million PY) drops below urothelial (2.1–3.7 cases/million PY) and squamous cell carcinoma (1.9–2.9 cases/million PY) [6].

PUC adenocarcinoma is observed more often in women than men and is thought to arise from Skene's ducts [36]. The two predominant histologic subtypes of

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adenocarcinoma are clear cell and columnar/mucinous. The clear cell subtype arises from the distal aspect of the duct and can be positive for prostate specific antigen (PSA) whereas the columnar/mucinous subtype arises from the proximal aspect of the duct, is similar to colonic or endocervical adenocarcinoma, and is carcinoembryonic antigen positive [37].

The majority of women diagnosed with PUC are symptomatic at the time of presentation, with greater than 70% of women reporting recurrent urinary tract infections, irritative voiding symptoms, or dyspareunia, while obstructive voiding and hematuria are less common presenting symptom [38].

3.1. Treatment of PUC in males

There are currently no treatment guidelines that specifically address urethral irritable bowel syndrome. However, urethral CIS is behaviourally life-threatening and may bear some biological resemblance to bladder CIS rather than penile CIS. In untreated urethral CIS, lymph node involvement occurs in half of the cases [29]. Surgical excision of the urethra to achieve negative margins can be performed as an appropriate management strategy whenever possible [30].

Dissection of the LN in the presence of detectable lymphadenopathy and other high-grade disease features such as lymphangiopathy is recommended and may result in a survival benefit [31].

Distal urethral tumours have significantly better survival rates than proximal tumours. In a previous study, penile-conserving surgery in patients with pT1-3N0-2 distal urethral carcinoma was not associated with local recurrence even with resection margins less than 5 mm [32]. In a retrospective study of 18 patients with tumours confined to the gastrointestinal tract, navicular fossa and urethra of the penis, penile-conserving surgery was performed and there was no local recurrence with a median follow-up of months out of 26 months [33] . However, some studies have shown that penile-conserving surgery may be associated with a higher risk of progression in patients with positive proximal margins, particularly those with lymphatic and perineural invasion of the primary tumor [34]. Therefore, organ-preserving therapy should only be offered to very select individuals based on a histopathological analysis of the proximal urethral material [35].

If the tumor was localized in the urethra, urethral resection with or without cystoprostatectomy should be performed in men. Transurethral resection may be appropriate for low-grade lesions. In the case of stage T2 lesions, complete penectomy and urethral resection with possible cystoprostatectomy and pelvic lymphadenectomy were required to allow local control of the disease [36]. However, despite these therapies, proximal UKA was associated with poor survival outcomes and progression to distant metastases within 6 months and required adjuvant and neoadjuvant chemoradiotherapy, particularly in CTS [37].

3.2. Treatment of PUC in females

3.2.1. Anterior Urethra

The extent of tumor involvement influences how anterior female PUC is managed. Small, distant urethral tumors may be treated with laser therapy or endoscopic resection. A different course of action for tiny, exophytic anterior urethral tumors is partial urethrectomy. Nevertheless, there is little evidence of local control using urethral sparing techniques with a single modality. Five-year crude survival was 64% and five-year disease-specific survival was 66%, according to a short observational research by DiMarco et al. urine continence difficulties were the most common, accounting for 42% of new cases of stress incontinence and 8% of cases of urine retention[41].

Treatment with surgery that spares the bladder has been reported for advanced anterior urethral tumors that are carefully chosen. This entails a transvaginal radical urethrectomy, with the bulbocavernosus muscles on both sides and all surrounding periurethral soft tissue from the pubic symphysis to the bladder neck as the limits of resection. A catheterizable route, such as an appendicovesicostomy, is subsequently constructed after the bladder neck is closed [42,41].Women with localized anterior PUC may have the best chance of a local cure with a radical urethrectomy.Women with localized anterior PUC may have the best chance of a local cure with a radical urethrectomy[43].

An appropriate organ-sparing substitute for surgery in PUC female patients is radiation therapy employing either radiation from an external beam therapy, brachytherapy, or both.Reference code 56 Anterior tumors have a 71–74% five-year survival

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rate[44,45].However, 16–49% of patients experience radiotherapy-related problems, which can be significant. Radiation cystitis, urethral stricture, vesicovaginal fistula, and perineal desquamation are a few examples of these consequences[44,46]

3.2.2. Posterior Urethra

Comparison with PUC of the anterior urethra, patients treated with surgery, radiation therapy, or a combination of these modalities had a worse five-year overall survival (54% vs.25%) and disease-specific survival (69% vs. 46%) for PUC involving the posterior female urethra [47].Surgery for anterior pelvic exenteration includes extended pelvic lymphadenectomy, hysterectomy, urethrectomy, cystectomy, and oophorectomy. With regard To obtain a negative margin, more vulva or vaginal resections might be required.An evaluation of the results of radical surgical therapy alone is challenging because some of the patients had adjuvant radiation and/or chemotherapy. A single study by Dalbagni et al. reported a median survival after cystectomy of 36 months. Another single institution series of 27 patients who underwent complete extirpative surgery noted a five-year crude and disease specific survival of 39% and 52% respectively [41].

It has been proposed that radiation monotherapy is an option to drastic surgery. Milosevic et al. discussed their experiences treating PUC women with external radiation both with and without brachytherapy. 56% of the 27 patients who were part of the study had involvement in the proximal urethra. Over the course of a median follow-up of 7.6 years, the relapse-free rate was 37% and the cause-specific survival was 20%. For women with proximal urethral involvement, advanced stage disease, or tumors expanding into surrounding organs, brachytherapy did not enhance cause-specific survival, although it did improve local control when combined with external radiation [46].Based on data gathered after surgery, there appears to be no difference in the rate of local recurrence after radiation therapy [47].

As previously stated, radiation therapy side effects are not unusual. Of the 55 women in an MD Anderson series with anterior or posterior PUC, 49% had problems related to radiation. In total, 20% of cases involved urethral stricture, 18% involved fistula or necrosis, and 11% involved cystitis or bleeding [44].

Women with advanced PUC may benefit most from multimodal therapy, which combines chemotherapy, radiation, and surgery; however, the precise combination or order of modalities needs to be determined. Neoadjuvant radiation plus surgery was proven to considerably increase local recurrence-free survival in the Dalbagni et al series [47].A study by Dayyani et al. that included a cohort of men (36%) and women (64%) with advanced PUC found that neoadjuvant platinum-containing chemotherapy regimens followed by surgery provided an overall survival benefit relative to chemotherapy alone. This was covered earlier (male bulbar urethra section). In particular, at the three-year follow-up, 44% of the nine patients who had lymph node metastases at the time of diagnosis were clear of illness [48].

4. Follow-up

The treatment of PUC patients necessitates follow-up, which should be targeted to each patient's unique risk factors. But no precise guidelines have thoroughly examined the surveillance regimes. Guidelines from the European Association of Urology have only suggested that patients undergoing urethra-sparing surgery should have a more thorough follow-up [38]. An out-patient visit, urine cytology, urethrocystoscopy, uroflow, and cross-sectional imaging were all part of the PUC surveillance protocol in one study. These procedures were performed 3-6 months following surgery and then every 6 months for a minimum of 2 years [39]. In another investigation, PUC patients were followed up on for a brief period of time, initially every 2-4 weeks at an outpatient clinic, and then every six months. A comprehensive follow-up program was implemented for patients who had extensive urethral restoration. This included laboratory testing, uroflow, regressive urethrography, and yearly urine cytology [40].

5. Conclusion

The tumour’s severity, clinical nature, and location should all be taken into consideration when managing PUC. Organ sparing techniques can be applied to individuals with superficial and distal urethral lesions, whereas an ideal multimodal treatment plan should be employed for patients with more advanced illnesses. Future multi-institutional collaborations should be held

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more frequently to look at more effective PUC treatment options.

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